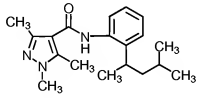
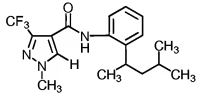
REMARKS

Applicants gratefully acknowledge withdrawal of the previous rejections under 35 U.S.C. 102 and 103 in view of previous amendments.

Applicants also acknowledge the statements in the Office Action at pages 2-5 about the scope of the examination, particularly with respect to examination of N-[2-(1,3-dimethylbutyl)phenyl]- 1,3,5-trimethyl-1H-pyrazole-4-carboxamide having the formula

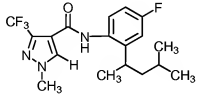


(which is identified in the Office Action at pages 3 and 5 as being free of prior art) and N-[2-(1,3-dimethylbutyl)phenyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide having the formula



which, it may be noted, differ in the definitions of groups R^9 and R^{10}.

Applicants have several observations about the scope of examination as presented in the Office Action. Applicants first note that the second compound identified above is specifically excluded by proviso (a) of Claims 11 and 12 (even before the current amendments) and is thus outside the scope of Applicants' claims. However, because the second compound was described as known prior art in the new obviousness rejection discussed below and because the new obviousness rejection clearly focuses on the structurally similar fluorinated compound N-[4-fluoro-2-(1,3-dimethylbutyl)phenyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide) having the formula



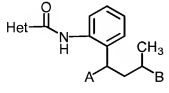
(referred to in the Office Action at pages 8 et seq as Compound A), Applicants assume that examination necessarily also extends to Compound A. For this and other reasons discussed below, Applicants have amended their claims to limit the subject compounds to those in which group R^2 is fluorine. [Proviso (a) is rendered redundant by this amendment and has been deleted.] As pointed out in the Office Action at page 8, Compound A is described in Example 12 at page 41 of Applicants' specification. Test data can be found in Table B (page 53), Table C (page 56), Table D (page 59), and Table E (page 62).

Applicants also note by way of comment with respect to the restriction requirement as characterized in the Office Action at page 2, Applicants' election was without traverse only with respect to Group II (i.e., canceled Claims 16 and 19) but was made with traverse with respect to Group III (i.e., withdrawn Claim 18). See Amendment dated June 10, 2008, at page 17). Claims 13 and 14 were withdrawn only because of a species election. Applicants have consistently requested rejoinder of all withdrawn claims. As to any subject matter not rejoined during the current examination, Applicants again reserve the right to file one or more divisional applications to the non-elected subject matter.

Rejection under 35 U.S.C. 103

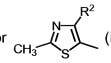
Claims 11-12 and 17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,914,344 ("Yoshikawa et al") in view of Patani et al, *Chem. Rev.*, 96, 3147-3176 (1996) ("Patani et al article"). Applicants respectfully traverse.

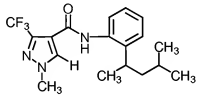
As fully discussed in Applicants Amendment dated January 26, 2010, Yoshikawa et al discloses carboxanilide derivatives of the formula



(where the formula is drawn in the same orientation as shown in Applicants' claims for clarity) in which **Het** can be one of the heterocyclic groups 

(III) (where R^1

is trifluoromethyl or difluoromethyl) or  (II2) (where R^2 is trifluoromethyl, difluoromethyl, or methyl); **A** is hydrogen or methyl, and **B** is methyl or ethyl (with the exclusion of compounds in which A is methyl and B is ethyl), as well as specified intermediates thereof. E.g., column 4, lines 1-67. Among the disclosed compounds is a compound having the formula

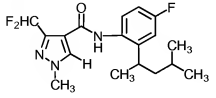


(referred to in the Office Action at page 8 as Compound B). Applicants again point out that the benzene ring of the disclosed carboxanilide derivatives for which fungicidal activity is taught does not bear any ring substituent other than the amide and alkyl moieties shown in the above formula. In contrast, the benzene ring of Applicants' claimed compounds must bear a further fluorine substituent, a characteristic not found in the compounds disclosed in the reference. See Applicants' previous Amendment at page 9 and the current Office Action at pages 3-4. Applicants therefore submit that Yoshikawa et al would not alone suggest their claimed invention.

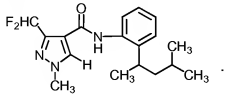
However, the Office Action at pages 8-9 relies on the Patani et al article to conclude that a hydrogen atom (such as on the benzene ring of Compound B of Yoshikawa et al) could be replaced with a fluorine atom (such as in Compound A of Applicants' invention) with the expectation that biological/pharmaceutical properties would not be altered. Applicants submit that the Patani et al article does not bridge the gap between Yoshikawa et al and their claimed invention. The Patani et al article beginning at page 3149 discusses several examples of bioisosterism relating to fluorine substitution, including some examples showing the interchangeability of hydrogen and fluorine (e.g., pages 3149-3150) and other examples showing the effect of replacing hydrogen with fluorine, hydroxyl, amino, or methyl groups (e.g., pages 3152-3155). However, the Patani et al article reveals that significant and unpredictable differences in biological activity can arise when making such changes. For example, **Figure 2 (Table 4)** shows an almost four-fold greater binding affinity

(as shown by a lower inhibitory concentration IC_{50}) when H is replaced by F in one naphthyl-fused diazepine but an almost twenty-fold greater binding affinity for a second naphthyl-fused diazepine. **Figure 3 (Table 5)** shows about 2.6 times greater anti-inflammatory activity for a difluoro androstane derivative compared to the monofluoro analog but only about 1.5 times greater anti-inflammatory activity for a related monofluoro androstane derivative compared to the dihydro analog having no fluoro substituent. Since both of the monofluoro compounds shown in Figure 3 have almost the same activity, one might expect that going from no fluorine to one fluorine and from one fluorine to two fluorines would result in a uniform increase in activity for each additional fluorine, but this was not the case. That is, in contrast to the dramatic increase in activity shown in Figure 2, only modest changes in activity are shown in Figure 3, but in each case the activities increase with fluorine substitution. **Figure 11 (Table 9)** bolsters Applicants' position. That is, in contrast to the increased biological activity found for the compounds shown in Figures 2 and 3, the fluorine-substituted test compound shown in Figure 11 (Table 9) exhibited about 1.6 times lower angiotensin converting enzyme activity and about 2.4 times lower endopeptidase activity (as shown by greater inhibitory concentration IC_{50} in each test). In short, the data in Figure 2 (Table 4) and Figure 3 (Table 5) showed variably enhanced activity when F replaces H, whereas the data in Figure 11 (Table 9) showed reduced activity when F replaces H. That is, a proper reading of the Patani et al article shows that the specific degree of activity was both variable and unpredictable from compound to compound and from test to test. Therefore, even if one assumes that hydrogen can sometimes be replaced by fluorine or fluorine by hydrogen, that does not mean that one skilled in the art would be able to predict what activity or level of activity would result.

In further support of their position, Applicants now present data in the form of Declarations under 37 C.F.R. 1.132 of Dr. Ulrike Wachendorff-Neumann and of Dr. Peter Dahmen showing unexpectedly enhanced biological activity of a fluorine-substituted compound of their invention disclosed in Example 14 of their specification and having the formula



compared with the corresponding unsubstituted comparison compound described in Example 3 of Yoshikawa et al and having the formula



In particular, in the *Leptosphaeria nodorum* test, Applicants' inventive compound exhibited an efficacy of 93%, whereas the comparison compound exhibited an efficacy of only 44%. Similarly in the *Sphaerotheca* test, Applicants' inventive compound exhibited an efficacy of 100%, whereas the comparison compound exhibited an efficacy of 78%. Although these compounds have a CHF_2 substituent on the pyrazole ring instead of a CF_3 group as found in Compounds A and B, Applicants submit that it is well established that even indirect comparisons, when "based on established scientific principles, can validly be applied to distinguish a claimed chemical process or product from that disclosed in the prior art." *In re Best, Bolton and Shaw*, 562 F.2d 1529, 195 U.S.P.Q. 430, 432 (C.C.P.A. 1977); see also *In re Blondel, Fouche, and Gueremy*, 499 F.2d 1311, 182 U.S.P.Q. 294 (C.C.P.A. 1974). Here, the only structural difference between the tested pair of compounds and the Compound A/Compound B pair is the presence of a CHF_2 group instead of a CF_3 group. Regardless of whether one might suppose that such a difference could conceivably have an effect on the results, Applicants have provided data in the specification showing that the inventive compound of Example 12 in which R^9 is CF_3 (i.e., Compound A) and the inventive compound of Example 14 in which R^9 is CHF_2 in fact exhibit almost identical activities in the tests reported in Table B (page 53), Table C (page 56), and Table D (pages 59 and 60, respectively). Applicants therefore submit that they have presented evidence showing that their invention is distinguishable from the cited references.

Applicants therefore respectfully submit that their claimed invention is not rendered obvious by Yoshikawa et al in view of the Patani et al article.

In view of the preceding amendments and remarks, allowance of the claims is respectfully requested.

Respectfully submitted,

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